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Review

The Genus *Psychotria*: Phytochemistry, Chemotaxonomy, Ethnopharmacology and Biological Properties

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Psychotria genus (Rubiaceae) is featured into the angiosperm, being the most speciose genus comprising approximately 1600 species. The available references demonstrate that *Psychotria* has several uses on traditional medicine including spiritual and cultural purposes, and presents great potential on pharmacological properties, especially the one related to neurodegenerative diseases. Despite its wide biological properties, this genus has shown complex phylogenetic analysis due to lack of chemotaxonomic information. In recent years, the interest in these plants has increased considerably and many active compounds have been isolated. Phytochemical investigations described in the literature confirmed the indole alkaloids as the major compounds and besides that, another particular chemical constituent are cyclic peptides, known as cyclotides. This present review will cover the relevant literature from 1962 until 2015, and outlines the current data on taxonomy, chemotaxonomy, traditional uses, pharmacological properties, chemical composition and ecological approach from *Psychotria* genus.

Keywords: *Psychotria*, alkaloids, chemotaxonomy, ethnopharmacology, phytochemistry

1. Introduction

It is believed that about 80% of the population worldwide, especially Asian and African countries use plants and herbal medicines as a source of medicinal agents and primary health care. Traditional medicine is an important form of health care for many people and covers a wide variety of therapies and practices, which vary from country to country.[1] Many useful drugs were inspired from plants sources and nature continues to be a major source of new structural leads, and effective drug development.[2] Thus, based on this estimates it is of great importance the proper identification and classification of plant species.

The genus *Psychotria* belongs to the Rubiaceae family (subfamily Rubioideae, tribe Psychotrieae) and is the most speciose angiosperm genera (flowering plants) comprising approximately 1600 species. These species are mostly shrubs, although are known, vines, herbaceous and epiphytes, widely distributed in tropical and pantropical countries.[3,4] In South America countries the leaves of *P. viridis* is largely used by Amazon indigenous peoples as a component of the hallucinogenic drink "ayahuasca". This tea has been used for medicinal, spiritual and cultural purposes since pre-Columbian times.[5-8] Some other plants from the genus *Psychotria* (leaves, roots and rhizomes) have been widely used in traditional medicines for treating bronchial and gastrointestinal disorders such as cough, bronchitis, ulcer and stomachache. Also, they are commonly used for infections of the female reproductive system.[9]

Besides the variety of ethnopharmacology uses the taxonomy of *Psychotria* genus is very complex and a comprehensive phylogenetic analysis of this genus lack diagnostic characters. Until now, schizocarps and bacterial leaf nodules have been used for recognizing formal groups in Psychotrieae, but a robust phylogeny of the tribe, including their evolution and taxonomic value have not been described.[10]

An increasing number of phytochemical studies have been investigated in *Psychotria* plants in the last decade contributing significantly to the ethnobotanical, pharmacological and chemotaxonomic studies in addition

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†*In memoriam*

to the molecular phylogenetic analysis.[11] The genus *Psychotria* can be characterized as an abundant source of indole, monoterpene indole, quinoline and isoquinoline alkaloids as well as flavonoids, coumarins, terpenoids and cyclic peptides that might be responsible for a wide range of biological activities (cytotoxicity, analgesics, antivirals, antifungals and modulators of the activity of the central nervous system) found on those species.[12,13]

The purpose of this review is to provide an update of the recent ethnopharmacology, taxonomy, chemotaxonomy, chemical approach, pharmacological and ecological properties of the extracts and isolated compounds identified in some plants belonging to the genus *Psychotria*.

2. Method

In the present review, information on *Psychotria* genus was gathered via searching scientific databases including PubMed, Elsevier, Google Scholar, Scopus, Web of Science, Cybase and SciFinder by using the keyword *Psychotria*.

In order to retrieve the available literature pertaining to this genus and concisely illustrate it using an informative graph, a SciFinder search was performed in September 2015. Figure 1 shows the number of articles retrieved when using the keyword *Psychotria* for year, which demonstrate the relevance of this genus. It is remarkable the large increase in publications in recent years; whereas in 1995 had been described about 10 scientific papers, in 2014 more than 50 scientific papers have been published on *Psychotria* genus and this number continues to increase in 2015.

3. Taxonomy and Chemotaxonomic Approach of Genus *Psychotria*

The tribes Palicoureeae and Psychotrieae include about 91% of the species of the Psychotrieae alliance and about 24% of Rubiaceae as a whole. Members of these groups of plants are very important components of various terrestrial ecosystems throughout the tropics. The tribe Psychotrieae is well established, but the same does not occur for their genera. The *Amaracarpus* Blume, *Calycosia* A. Gray, *Dolianthus* C. H. Wright, *Hedstromia* A. C. Sm., and *Hydnophytum* Jack genera, for example, were nested within *Psychotria* L. rendering the latter genus paraphyletic.[10]

Before 2014, the relationships between among most members of tribes Psychotrieae and Palicoureae were still unknown partly, due to the poor or lack of sampling from some biodiversity hotspots. Schizocarpous fruits and bacterial nodules were used for recognizing authentic groups, but the evolution and taxonomic value of these characters have not been addressed based on a broadened sampling of the tribe.

In 2014, a robust phylogenetic study was done for establishing new generic circumscriptions between these tribes. Razafimandimbison *et al*.[10] established that *Psychotria* includes all its allied genera, rendering the tribe Psychotrieae monogeneric. It was confirmed the paraphyly of *Psychotria*, because the genera *Amaracarpus*, *Calycosia*, *Camptopus*, represented by its type *C. mannii* (= *P. camptopus*), *Dolianthus*, *Hydnophytum*, *Grumilea* Gaertn., represented by the type *G. nigra* (= *Psychotria nigra*), *Mapouria*, and all the WIOR genera (*Apomuria*, *Cremocarpon*, *Psathura*, *Pyragra*, and *Trigonopyren*) are nested within a broadly defined *Psychotria*.[10]

A great variety of species of plants belonging to the genus *Psychotria* have been phytochemically investigated and several compounds have been isolated and identified. Thus, the phytochemical approach, which involves a range of compounds, became a very useful tool to understand and establish the chemotaxonomy of *Psychotria*. In this context, different classes of organic compounds have been reported.[11]

Analysis of the chemical profile of some species like *P. borucana* contributed to the taxonomic rearrangement, which was grouped together with *P. ipecac* in *Carapichea* genus.[14] The comparative study of 57 methanol extracts of

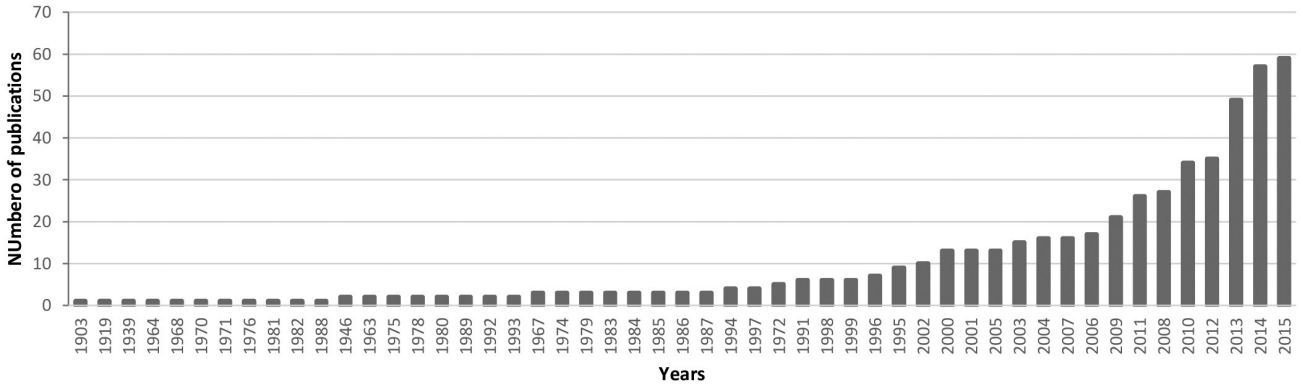


Figure 1. Results of SciFinder search for *Psychotria* genus publications up to 2015.

Psychotria clearly showed a distinct chemical separation of *P. borucana* due to the bigger accumulation of alkaloids type dopamine-iridoid rather than alkaloids type tryptamine-iridoid, which is commonly found in other species. In this context stands out the borucoside alkaloid (**1**), which was first described in this species.[14]

As an example, the species *Psychotria acuminata* was renamed to *Palicourea acuminata* (Benth.) and from methanol extract of its leaves and stem bark, were isolated several alkaloids type tryptamine-iridoids. Among those structures, lagamboside (**2**) is a novelty because represents an unusual pattern of *N*-glycosylation and a iridoid closely related to the unusual alkaloid vallesiachotamine (**3**).[15] Also, the co-occurrence of another rare alkaloid, the bahienoside B (**4**), comprising two iridoids structures, is of great interest and contributes to the chemotaxonomy of this species (Figure 2).[16]

Besides the alkaloids, some other secondary metabolites also can be used as taxonomic markers. Vomifoliol (**5**), for example, is a megastigmane sesquiterpene that has been reported on *Psychotria gitingensis* from the Philippines. This compound has an α,β-unsaturated ketone that might be responsible for the observed orange spots in Dragendorff's test.[17] It is well established that certain compounds can give false-positive alkaloid reactions with Dragendorff's spray reagent.[18]

Although *P. gitingensis* from Philipines did not present alkaloids, is highly recommended to verify the absence of alkaloids in species collected in other regions.

4. Traditional Uses of *Psychotria* Species

Plants from the genus *Psychotria* (leaves, roots, barks and rhizomes) are commonly used in traditional medicines for treating bronchial and gastrointestinal disorders such as cough, bronchitis, ulcer and stomachache. Also they are used for infections of the female reproductive system.[9,19,20] *P. poeppigiana* is a native plant widely used in Latin America for the treatment of a variety of diseases, particularly gastrointestinal disorders, stomachaches and fever.[21] In Panama, this plant is also used in traditional medicine for the treatment of dyspnea.[22] *P. colorata* is a plant commonly found in Amazon region of Brazil, which is used as painkiller for earache and abdominal pain by traditional rural communities.[23]

In Tamil Nadu (India) several tribes use the leaves, flowers and fruits from *P. nudiflora* Wt. & Arn. and *P. nilgiriensis* Deb. & Gan for rheumatism treatment.[24] Other applications are anti-emetic and against snakebites in Central and South America countries.[25,26] In S. Tomé and Príncipe (Africa), *P. subobliqua* is used to treat toothaches and mouth inflammation.[27,28]

P. ipecacuanha (Brot.) Stokes is another species important on traditional medicine. It has an important history as emetic, expectorant, amebicide and also in the treatment of dysenteries.[29] Besides the properties already described, some *Psychotria* species are also used against microbial infections (malaria, amoebiasis, viral and venereal diseases), cardiovascular and mental disorders.[30,31]

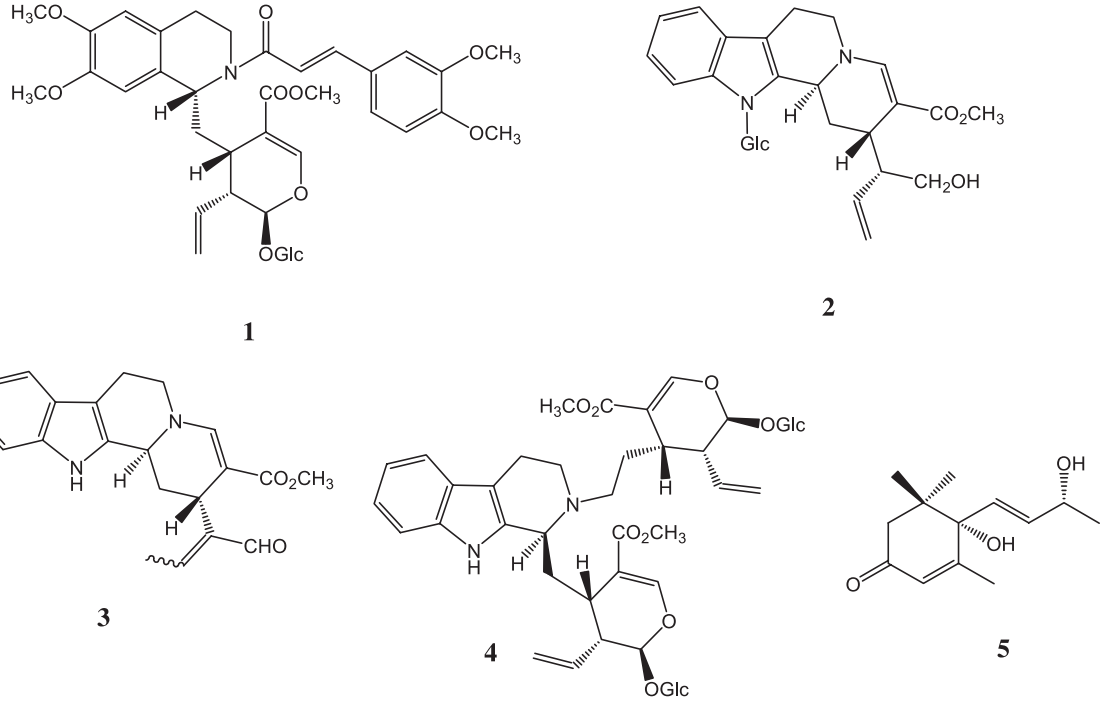


Figure 2. The structures from *Psychotria* genus.

In South America countries (Brazil, Peru and Ecuador) some species from the genus *Psychotria* are largely used by Amazon indigenous people as a component of the hallucinogenic drink "ayahuasca" which means "soul wine", used in religious ceremonies.[5-8] "Ayahuasca's" psychoactive effects are similar to LSD (lysergic acid diethylamide) and psilocybin.[8] The" ayahuasca" tea usually incorporates the leaves of *P. viridis* and bark of *Banisteriopsis caapi*, which are rich in *N*,*N*-dimethyltryptamine (a non-selective serotonin agonist, 5-HT) and β-carboline alkaloids, respectively.[32-34] A qualitative empirical study made by Anja and Rolf[35] explored the ritual use of "ayahuasca" in the treatment of addictions. The recently findings indicate that "ayahuasca" can serve as a therapeutic tool which catalyze neurological and psychological processes that support recovery from substance dependencies.

Some *Psychotria* species distributed in China are used in folk medicines for swelling and relieving muscles, activating collaterals and strengthening bones and muscles.[36] *P. henryi* is one of these species that has been used in traditional Chinese medicine for invigorating spleen to eliminate dampness and for regulating qi-flowing to relieve pain.[37]

5. Chemical Constituents of Genus *Psychotria*

In recent years, the interest in plants from *Psychotria* genus has increased considerably, since it is an abundant source of several interesting natural products as alkaloids (major compounds), coumarins, flavonoids, terpenoids, tannins and cyclic peptides (Tables 1 and 2).

Table 1. Compounds identified from *Psychotria* species[a]

Specie and synonymia[b]	Compound	Reference
P. acuminate Synonymia: *Palicourea acuminata* (Benth.) Borhidi; = *Psychotria cuspidata* Bredem. ex Schult.	strictosidinic acid (**11**)	16
	strictosidine	16
	palicoside	16
	bahienoside B (**4**)	16
	5α-carboxystrictosidine (**34**)	16
	desoxycordifoline	16
	lagamboside (**2**)	16
	vallesiachotamine (**3**)	16
P. adenophylla Wall. Synonymia: *Grumilea adenophylla* (Wall); = *Psychotria connata* Kurz; = *Psychotria siamensis* Ridl.; = *Uragoga adenophylla* (Wall.) Kuntze.	bauerenol	38
	bauerenol acetate	38
	friedelin	38
	betulin	38
	betulinic acid	38
	α-amyrin	38
	ursolic acid (**94**)	38
	β-sitosterol (**71**)	38
P. bahiensis DC Synonymia: *Declieuxia psychotrioide* DC.; = *Palicourea didymocarpa* (*A. Rich.* ex DC.) *Griseb.*; = *Psychotria cuspidata var. bahiensis* (DC.) Müll. Arg*;* = *Psychotria didymocarpos* (*A. Rich* ex DC.) *Lemée*; = *Psychotria diplosphaerica Müll. Arg*.; = *Ronabea didymocarpos A. Rich.* ex DC.; = *Uragoga bahiensis* (DC.) Kuntze.	bahienoside A (**33**)	39
	bahienoside B (**4**)	39
	5α-carboxystrictosidine (**34**)	39
	angustine (**35**)	39
	strictosamide (**22**)	39
	vallesiachotamine (**3**)	39
P. barbiflora DC Synonymia: *Psychotria hoffmannseggiana* (Willd. ex Schult.) Müll. Arg.	harmane (**10**)	40
	strictosidinic acid (**11**)	40
P. beccarioides Wernham Synonymia: *Psychotria leptothyrsa* Miq.	psychotridine (**42**)	41
P. borucana (Ant. Molina) C. M. Taylor & W. Burger Synonymia: *Carapichea affinis* (Standl.) L. Andersson	cephaeline (**30**)	14
	emetine (**12**)	14
	ipecoside	14
	6-*o*-methylipecoside	14
	6-*o*-methyl-*trans*-cephaeloside	14
	borucoside (**1**)	14
P. brachyceras Müll. Arg. Synonymia: *Uragoga brachyceras* (Müll. Arg.) Kuntze.	brachycerine (**14**)	42

Table 1. Compounds identified from *Psychotria* species[a] (cont.)

Specie and synonymia[b]	Compound	Reference
P. cadigensis Merr.	vomifoliol (**5**)	43
	loliolide (**61**)	43
	isololiolide (**64**)	43
P. calocarpa Kurz Synonymia: *Psychotria viridiflora* var. *undulata* Kurz; = *Uragoga picta* Kuntze.	psychotriasine (**16**)	44
P. camponutans (Dwyer & M. V. Hayden) Hammel Synonymia: *Notopleura camponutans* (Dwyer & M. V. Hayden) C. M. Taylor.	1-hydroxybenzoisochromanquinone (psychorubrin) (**86**)	45
	benz[*g*]isoquinoline-5,10-dione (**87**)	45
P. colorata (Willd. ex Roem. & Schult) Müll. Arg. Synonymia: *Cephaelis amoena* Bremek; = *Cephaelis colorata* Willd. ex. Roem.; = *Cephaelis glabrescens* (Müll. Arg.) Standl.; = *Psychotria calviflora* Steyerm.; = *Psychotria glabrescens* Müll. Arg.; = *Psychotria megapontica* Müll Arg.; = *Uragoga colorata* (Willd. ex Schult) Kuntze; = *Uragoga glabrescens* Müll. Arg.) Kuntze; = *Uragoga megapontica* (Müll. Arg.) Kuntze.	8-8*a*, 8'-8'*a* tetradehydroisocalycanthine 3a(*R*), 3*a*'(*R*)	46, 47
	calycanthine (**56**)	46, 47
	isocalycanthine (**57**)	46, 47
	(+)-chimonanthine	46, 47
	meso-chimonanthine (**37**)	46, 47
	N_b-desmethyl-*meso*-chimonanthine (**38**)	46, 47
	hodgkinsine (**39**)	46, 47
	quadrigemine B (**89**)	46, 47
	quadrigemine C (**40**)	46, 47
	psychotridine (**42**)	46, 47
P. correae (Dwyer & M. V. Hayden) C. M. Taylor Synonymia: *Cephaelis correae* Dwyer & M. V. Hayden.	isodolichantoside (**49**)	48
	correantoside (**50**)	48
	correantine A (**52**)	48
	correantine B (**53**)	48
	20-epi-correantine B (**55**)	48
	correantine C (**54**)	48
	10-hydroxycorreantoside (**51**)	48
	megastigm-5-ene-3,9-diol	48
	S(+)-dehydrovomifoliol	48
	lutein	48
	rotungenic acid	48
	clethric acid	48
	daucosterol	48
	stigmasterol glucoside (**72**)	48
	cerebroside B_{1b}	48
	cerebroside	48
P. euricarpa Standl. Synonymia: *Palicourea eurycarpa* (Standl.) C. M. Taylor.	linalool	49
	methyl salicylate	49
P. forsteriana A. Gray Synonymia: *Psychotria forsteriana* var. *vitiensis* A. Gray; = *Uragoga forsteriana* (A. Gray) Drake.	calycanthine (**56**)	50
	iso-calycanthine (**57**)	50
	meso-chimonanthine (**37**)	50
	quadrigemine A (**88**)	51
	quadrigemine B (**89**)	51
	psychotridine (**42**)	51
	isopsychotridine B (**41**)	51
	quadrigemine G	52
	quadrigemine H	52
	hodgkinsine (**39**)	52
	isopsychotridine C (**90**)	
	isopsychotridine D	52
	isopsychotridine E	52
	vatine (**91**)	52
	vatamine (**92**)	52
	vatamidine (**93**)	52

Table 1. Compounds identified from *Psychotria* species[a] (cont.)

Specie and synonymia[b]	Compound	Reference
P. gitingensis Elmer Synonymia: *Grumilea similis* (Elmer) Merr.; = *Grumilea versicolor* (Elmer) Merr.; = *Psychoria lucida* Merr.; = *Psychotria similis* Elmer; = *Psychotria versicolor* Elmer.	vomifoliol (**5**)	17
P. glomerulata (Donn.Sm.) Steyerm. Synonymia: *Cephaelis glomerulata* Donn. Sm.; = *Palicourea glomerulata* (Donn. Sm.) Borhidi.	glomerulatine A (**46**)	53
	glomerulatine B (**47**)	53
	glomerulatine C (**48**)	53
P. haianensis H. L. Li	β-sitosterol (**71**)	54
	stearic acid	54
	quercetin (**73**)	54
	rutin (**77**)	54
	daucosterol	54
P. henryi H. Lév.	psychohenin (**13**)	55
P. ipecacuanha (Brot.) Stokes Synonymia: *Carapichea ipecacuanha* (Brot.) L. Anderson.	emetine (**12**)	56
	cephaeline (**30**)	57
	ipecoside	57
P. klugii Standl.	klugine (**28**)	58
	7'-*o*-demethylisocephaeline (**29**)	58
	cephaeline (**30**)	58
	isocephaeline (**31**)	58
	7-*o*-methylipecoside (**32**)	58
	emetine (**12**)	58
P. laciniata Vell. Synonymia: *Psychotria kleinii* L. B. Sm. & Downs; = *Uragoga laciniata* (Vell.) Kuntze.	strictosamide (**22**)	59
	lyaloside (**26**)	59
	vallesiachotamine (**3**)	59
	angustine (**35**)	60
	vallesiachotamine lactone (**85**)	60
	pauridianthoside	60
P. leiocarpa Cham. & Schltdl. Synonymia: *Psychotria constricta* Müll. Arg.; = *Psychotria extratropica* Müll. Arg.; = *Psychotria lagoensis* Müll. Arg.; = *Psychotria nitidula* Cham. & Schltdl.; = *Psychotria psilogyne* Müll. Arg.; = *Psychotria tenella* Müll. Arg.	asperuloside	61
	deacetylasperuloside	61
	N,β-*D*-glucopyranosyl vincosamide (**15**)	62
	bicyclogermacrene	63
	germacrene	63
P. leptothyrsa Miq. Synonymia: *Psychotria beccarii* (K. Schum.) K. Schum.; = *Psychotria beccarioides* Wernham; = *Psychotria montana* var. *gracillima* Wernham; = *Psychotria pedicellata* Valeton; = *Psychotria rugosa* Valeton; = *Psychotria salmoneiflora* K. Schum.; = *Psychotria schraderbergiensis* Valeton; *Uragoga beccarii* (K. Schum.) Kuntze.	psyles A-F	64
P. longipes Müll. Arg. Synonymia: *Psychotria vellosiana* Benth.	cyclopsychotride A	65
P. lyciiflora (Baill.) Schltr. Synonymia: *Uragoga lyciiflora* Baill.	*meso*-chimonanthine (**37**)	66
	hodgkinsine (**39**)	66
	N_b-desmethyl-*meso*-chimonanthine (**38**)	66
P. malayana Jack Synonymia: *Chassalia expansa* Miq.; = *Grumilea aurantiaca* (Wall.) Miq.; = *Psychotria aurantiaca* Wall.; = *Psychotria stipulacea* Wall.; = *Uragoga malayana* (Jack) Kuntze	(+)-chimonanthine	67
	(−)-chimonanthine	67
	meso-chimonanthine (**37**)	67
	calycanthine (**56**)	67
	hodgkinsine (**39**)	67
	2-ethyl-6-methylpyrazine	67
	3-methyl-1,2,3,4-tetrahydro-gamma-carboline	67
P. mariniana (Cham. & Schltdl.) Fosberg Synonymia: *Coffea mariniana* Cham. & Schltdl.; = *Psychotria hawaiiensis* var. *glabrithyrsa* Fosberg; = *Straussia mariniana* (Cham. & Schltdl.) A. Gray	β-sitosterol (**71**)	68
	betulin	68
	lupeol (**66**)	68
	ursolic acid (**94**)	68
	asperuloside	68

Table 1. Compounds identified from *Psychotria* species[a] (cont.)

Specie and synonymia[b]	Compound	Reference
P. myriantha Müll. Arg.	strictosidinic acid (**11**)	69
	myrianthosine	70
P. nuda (Cham. & Schltdl.) Wawra Synonymia: *Cephaelis nuda* Cham. & Schltdl.; = *Psychotria brasiliensis* Vell.; = *Psychotria hirtipes* Müll. Arg.; = *Psychotria involucellaris* Müll. Arg.; = *Psychotria multicolor* Müll. Arg.; = *Psychotria obfuscata* Müll. Arg.; = *Suteria brasiliensis* (Vell.) Mart.; = *Suteria macrantha* Gardner; = *Uragoga brasiliensis* (Vell.) Kuntze; = *Uragoga hirtipes* (Müll. Arg.) Kuntze.	srictosamide (**22**)	71
P. oleoides (Baill.) Schltr. Synonymia: *Uragoga oleoides* Baill.	hodgkinsine (**39**)	66, 72
	quadrigemine C (**40**)	66, 72
	isopsychotridine A	66, 72
	isopsychotridine B (**41**)	66, 72
	psychotridine (**42**)	66, 72
	quadrigemine I (**43**)	66, 72
	oleoidine (**44**)	66, 72
	caledonine (**45**)	66, 72
	psycholeine (**105**)	66, 72
P. pilífera Hutch**.**	psychotripine (**23**)	73
P. prunifolia (Kunth) Steyerm. Synonymia: *Cephaelis microcephala* Wild. ex Schult.; = *Cephaelis prunifolia* Kunth; = *Psychotria xanthocephala* Müll. Arg.; = *Tapogomea prunifolia* (Kunth) Poir.; = *Uragoga fuscostipulata* Kuntze; =*Uragoga microcephala* (Wild. Ex Schult) Kutze; = *Uragoga prunifolia* (Kunth) Kuntze; = *Uragoga xanthocephala* (Müll. Arg.) Kuntze.	10-hydroxyisodeppeaninol (**19**)	74, 75
	10-hydroxy-antirhirine	74, 75
	10-hydroxyantirhine *N*-oxide (**20**)	74, 75
	14-oxoprunifoleine (**21**)	74, 75
	prunifoleine (**84**)	74, 75
	strictosamide (**22**)	74, 75
P. rostrata Blume Synonymia: *Chassalia rostrata* (Blume) Miq.; = *Polyozus acuminata* Blume; = *Polyozus latifolia* Blume; = *Uragoga rostrata* (Blume) Kuntze.	quadrigemine B	76
	psychotrimine (**17**)	77
	psychopentamine (**18**)	77
P. rubra (Willd. ex Schult.) Müll. Arg. Synonymia: *Psychotria hoffmannseggiana* (Willd. Ex Schult.) Müll. Arg.	helenalin	78
	psychorubrin (**86**)	78
	psyrubrin A	79
	6-hydroxy-luteolin-7-*o*-rutinoside (**75**)	79
	luteolin-7-*o*-rutinoside (**76**)	79
	6α-hydroxygeniposide	79
P. serpens L. Synonymia: *Grumilea serpens* (L.) K. Schum.; = *Psychotria scandens* Hook. & Arn.; = *Psychotria serpens* var. *latifolia* Pit.; = *Uragoga serpens* (L.) Kuntze.	ursolic acid (**94**)	80
	rutin (**77**)	81
	quercetin (**73**)	81
	tamarixetin-3-*o*-rutinoside (**78**)	81
	kaempferol (**79**)	81
P. spectabilis Steyerm. Synonymia: *Cephaelis duckei* Standl.	deoxysolidagenone (**104**)	13
	solidagenone (**103**)	13
	coumarin (**81**)	13
	umbelliferone (**82**)	13
	psoralene (**83**)	13
	quercetin (**73**)	13
	quercetrin (**74**)	13

Table 1. Compounds identified from *Psychotria* species[a] (cont.)

Specie and synonymia[b]	Compound	Reference
P. stachyoides Benth. Synonymia: *Psychotria hygrophiloides* Benth.; = *Psychotria mesotropa* Müll. Arg.; = *Psychotria purpurascens* Müll. Arg.; = *Uragoga hygrophilodes* (Benth.) Kuntze; = *Uragoga mesotropa* (Müll. Arg.) Kuntze; = *Uragoga purpurascens* (Müll. Arg.) Kuntze; = *Uragoga stachyoides* (Benth.) Kuntze.	stachyoside (**24**)	82
	nor-methyl-23-oxo-correantoside (**25**)	82
	correantosine E	82
	correantosine F	82
	N-demethylcorreantoside	12
	bizantionoside B	12
	α-amyrin	12
	alizarine methyl-ether	12
	rubiadine	12
	scopoletin (**80**)	12
	barbinevic acid	12
	daucosterol	12
	stigmasterol glucoside (**72**)	12
P. suerrensis Donn. Sm.	harmane (**10**)	83
P. suterella Müll. Arg. Synonymia: *Psychotria estrellana* Müll. Arg.; = *Psychotria estrellana* var. *lanceolata* Müll. Arg.; = *Suteria parviflora* Gardner; = *Uragoga estrellana* (Müll. Arg.) Kuntze; = *Uragoga suterella* (Müll. Arg.) Kuntze.	lyaloside (**26**)	84, 59
	strictosamide (**22**)	84, 59
	naucletine (**27**)	84, 59
	vallesiachotamine (**3**)	84, 59
	cyclotide PS-1	85
P. umbellata Vell. Synonymia: *Psychotria brachyopoda* (Müll. Arg.) Britton	psychollatine	86, 87
	umbellatine (**6**)	86, 88
	3,4-dehydro-18,19-β-epoxy-psycholatine (**7**)	88
	N_4-[1-((*R*)-2-hydroxypropyl)]-psycholatine (**8**)	88
	N_4-[1-((*S*)-2-hydroxypropyl)]-psycholatine (**9**)	
P. vellosiana Benth. Synonymia: *Cephaelis attenuata* Miq.; = *Coffea sessilis* Vell.; = *Psychotria caloneura* Müll. Arg.; = *Psychotria hancorniifolia* Benth; = *Psychotria longipes* Müll. Arg.; = *Psychotria sororopanenensis* Standl. & Steyerm.; = *Psychotria velutipes* Müll. Arg.; *Uragoga caloneura* (Müll. Arg.) Kuntze; *Uragoa hancornifolia* (Benth.) Kuntze; *Uragoga interjecta* (Müll. Arg.) Kuntze; *Uragoga janeirensis* (Müll. Arg.) Kuntze; *Uragoga longipes* (Müll. Arg.) Kuntze; = *Uragoga pachyneura* (Müll. Arg.) Kuntze.	squalene (**65**)	89
	lupeol (**66**)	89
	stigmasterol (**68**)	89
	sitosterol (**67**)	89
	scopoletin (**80**)	89
P. viridis Ruiz & Pav. Synonymia: *Palicourea viridis* (Ruiz & Pav.) Schult.; = *Psychotria glomerata* Kunth; = *Psychotria microdesmia* Oerst.; = *Psychotria trispicata* Griseb.; = *Uragoga glomerata* (Kunth) Kuntze; = *Uragoga microdesmia* (Oerst.) kuntze; = *Uragoga trispicata* (Griseb.) Kuntze; *Uragoga viridis* (Ruiz & Pav.) Kuntze.	harmine	90
	harmaline	90
	tetrahydroharmine	90
	N,*N*-dimethyltryptamine (**36**)	91, 90, 92
P. yunnanensis Hutch. Synonymia: *Psychotria kwangsiensis* H. L. Li.	blumenol A	93
	drummondol	93
	3β-hydroxy-5α,6α-epoxy-7-megastigmen-9-one	93
	(−)-loliolide	93
	(6*S*)-menthiafolic acid	93
	salicylic acid	93
	resorcinol	93
	4-hydroxybenzoic acid	93
	vanillic acid	93
	syringic acid	93
	ethyl protocatechuate	93
	3-hydroxy-1-(3,5-dimetoxy-4-hydroxyphenyl) propan-1-one	93
	β-hydroxypropiovanillone	93
	(+)-syringaresinol	93
	2-(4-hydroxy-3-metoxyphenyl)-3-(2-hydroxy-5-methoxyphenyl)-3-oxo-1-propanol	93
	(−)-butin	93
	psycacoraone A (**63**)	36

[a]*Psychotria* species are organized in alphabetical order; [b]the synonym were obtained from references and reference 94.

5.1. Alkaloids

Several classes of alkaloids found on *Psychotria* genus is already described in the literature and some others are still under investigation (Figure 3).

A phytochemical study of *P. umbellata* Thonn. resulted in the isolation of psychollatine (umbellatine) (**6**) and other three psychollatine-derived monoterpene indole alkaloids: 3,4-dehydro-18,19-β-epoxy-psychollatine (**7**), *N*4-[1-((*R*)-2-hydroxypropyl)]-psychollatine (**8**), and *N*4-[1-((*S*)-2-hydroxypropyl)]-psychollatine (**9**).[86,88] Two β-carboline alkaloids (harmane (**10**) and strictosidinic acid (**11**)) were isolated from the leaves and stems of *P. barbiflora* DC.[95] Ipecac alkaloids are secondary metabolites produced in the medicinal plant *P. ipecacuanha* and emetine (**12**) is the main alkaloid found in syrup of Ipecac.[96] From the leaves and twigs of *P. henryi*, a new dimeric indole alkaloid, named psychohenin (**13**), was isolated.[97] Studies describe the presence of a monoterpene indole alkaloid, brachycerine (**14**), in the leaves and inflorescences of *P. brachyceras*.[42,97] From the leaves of *P. leiocarpa* Cham. & Schltdl. was obtained the major indole alkaloid *N*,β-*D*-glucopyranosyl vincosamide (**15**).[62,98] Psychotriasine (**16**) was isolated from the leaves of *P. calocarpa.* This compound is the first example of a dimeric tryptamine-related alkaloid that contains a free *N*-methyltryptamine unit in the molecule.[44] Two tryptamine-related alkaloids, psychotrimine (**17**) and psychopentamine (**18**), were isolated from the leaves of *P. rostrata*.[77] The crude extracts from the roots and branches of *P. prunifolia* led to the isolation of several alkaloids such as 10-hydroxyisodeppeaninol (**19**), 10-hydroxyantirhine *N*-oxide (**20**), 14-oxoprunifoleine (**21**) and strictosamide (**22**).[74] From the leaves of *P. pilifera* was isolated the compound psychotripine (**23**), a trimeric pyrroloindoline derivative with a hendecacyclic system bearing a hexahydro-1,3,5-triazine unit.[73] The aerial parts of *P. stachyoides* led the isolation of two monoterpene indole alkaloids, stachyoside (**24**) and nor-methyl-23-oxo-correantoside (**25**).[82] From the leaves of *P. suterella* Mull. Arg. were obtained three indole monoterpene alkaloids, lyaloside (**26**), naucletine (**27**) and strictosamide (**22**).[84] From the leaves of *P. nuda* was isolated a major compound named strictosamide (**22**).[71] *P. klugii* yielded two new benzoquinolizidine alkaloids, klugine (**28**), and 7'-*o*-demethylisocephaeline (**29**), together with the previously known cephaeline (**30**), isocephaeline (**31**), and 7-*o*-methylipecoside (**32**).[58] Two bis(monoterpenoid) indole alkaloid glucosides, bahienoside A (**33**) and bahienoside B (**4**), together with the known compounds 5α-carboxystrictosidine (**34**), angustine (**35**), strictosamide (**22**), and vallesiachotamine (**3**), were isolated from the aerial parts of *P. bahiensis*.[39] Dimethyltryptamine (**36**) was identified in the leaves of *P. viridis*, known for its ethnobotanical use as a hallucinogen.[91] *P. lyciiflora* and *P. oleoides*, led to the isolation of several pyrrolidinoindoline alkaloids. Two dimers, the known *meso*-chimonanthine (**37**), N_b-desmethyl-*meso*-chimonanthine (**38**), and hodgkinsine (**39**), have been isolated from *P. lyciiflora*. Hodgkinsine (**39**), quadrigemine C (**40**), isopsychotridine B (**41**), psychotridine (**42**), quadrigemine I (**43**), oleoidine (**44**) and caledonine (**45**) were obtained from *P. oleoides*.[66] From the aerial parts of *P. glomerulata* were isolated three quinoline alkaloids such as glomerulatine A (**46**), B (**47**) and C (**48**).[53] From extracts of the leaves and the roots of *P. correae* were obtained isodolichantoside (**49**) and the alkaloids correantoside (**50**), 10-hydroxycorreantoside (**51**), correantine A (**52**), B (**53**), and C (**54**), and 20-epi-correantine B (**55**).[48] *P. forsteriana* afforded three alkaloids (−)-calycanthine (**56**), iso-calycanthine (**57**), and *meso*-chimonanthine (**38**), a dimeric indole isomeric.[50]

5.2. Terpenoids

The phytochemical study on *P. yunnanensis* allowed the isolation of four norisoprenoids (**58-61**) and one monoterpenic acid (**62**). From the aerial parts of this plant a new type of sesquiterpene derived from acorane, possessing rare spirobicyclic carbon skeleton, known as psycacoraone A, was identified (**63**).[36,93]

From the leaves of *P. cadigensis*, an endemic species from Philippines, were isolated three nor-sesquiterpenes: vomifoliol (**5**), loliolide (**61**) and isololiolide (**64**). This was the first time that the phytochemical study of this species was described in the literature.[43] In *P. vellosiana* Benth. was reported the presence of squalene (**65**), lupeol (**66**), a mixture of sitosterol (**67**) and stigmasterol (**68**) obtained from the aerial parts of the plant. Also according to the authors this is the first time that squalene was described on the genus.[89] From the floral essential oil of *P. eurycarpa* Standl. were obtained some components such as linalool (**69**) and α-terpineol (**70**).[49] The extract from leaves and roots of *P. stachyoides* Benth. provided β-sitosterol (**71**) and stigmasterol glucosides (**72**) (Figure 4).[12]

5.3. Flavonoids

P. carthagenensis, *P. leiocarpa*, *P. capillacea* and *P. deflexa* were investigated in order to found total phenolics, flavonoids, condensed tannins and flavonols in their composition. Among these species, the highest flavonoid concentration was found in *P. carthagenensis* and *P. capillacea* extracts.[20] Similar studies were done for *P. hainanensis* and *P. nilgiriensis* fruit and, both

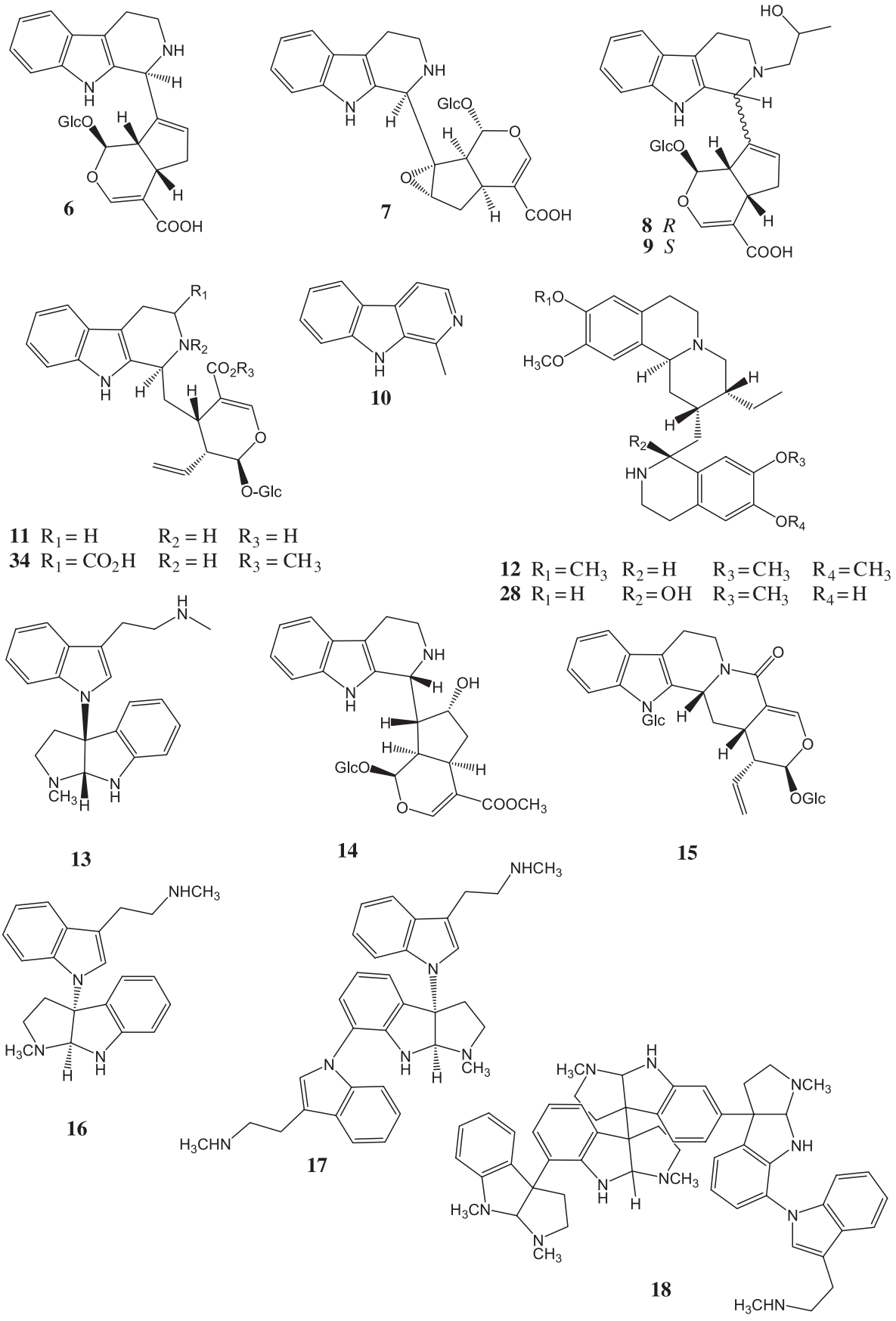
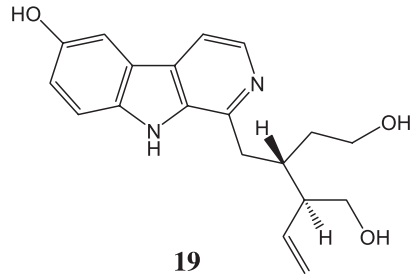


Figure 3. The structures of alkaloids from *Psychotria* species.



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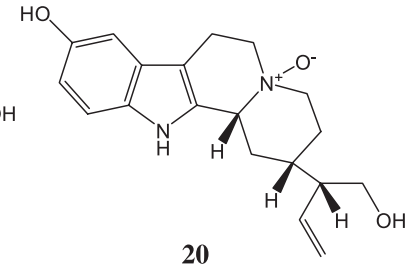

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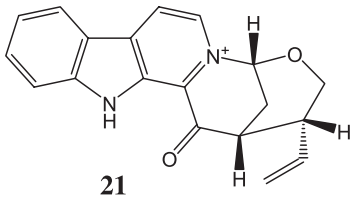

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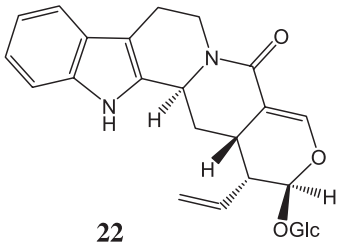

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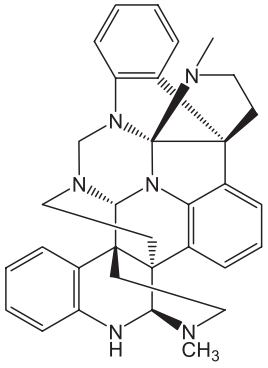

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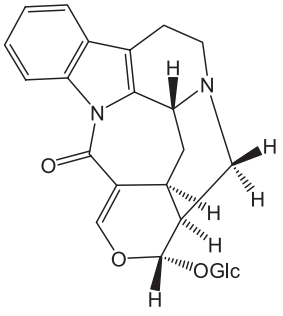

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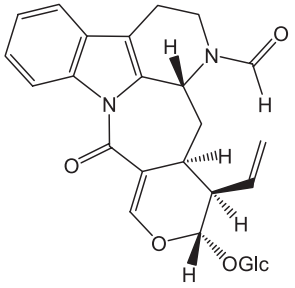

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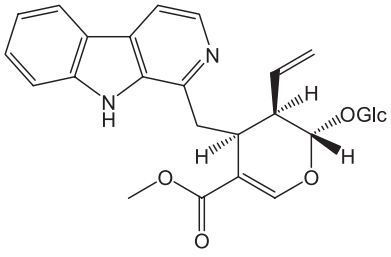

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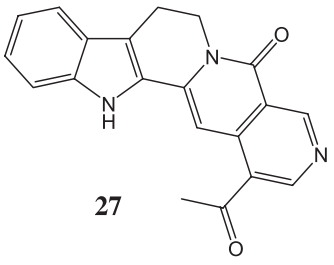

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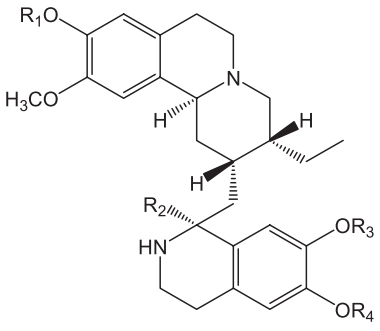
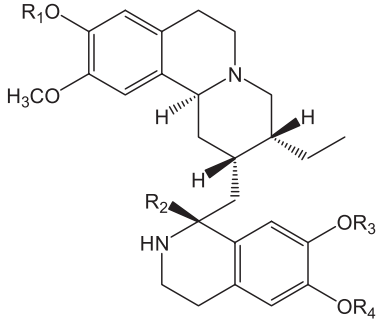
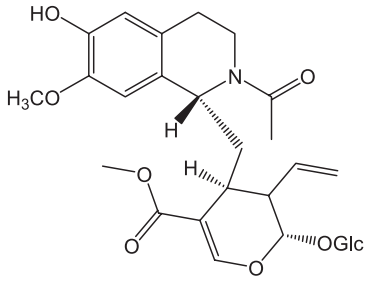


29 $R_1 = CH_3$ $R_2 = H$ $R_3 = H$ $R_4 = H$
31 $R_1 = CH_3$ $R_2 = H$ $R_3 = CH_3$ $R_4 = H$



30 $R_1 = CH_3$ $R_2 = aH$ $R_3 = CH_3$ $R_4 = H$



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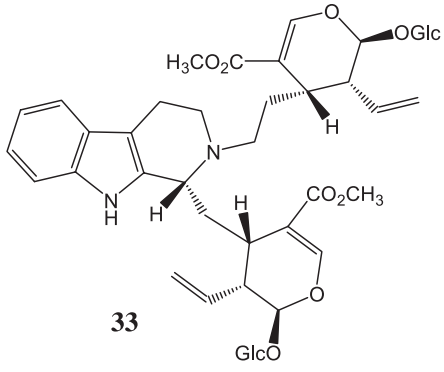

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Figure 3. The structures of alkaloids from *Psychotria* species (cont.).

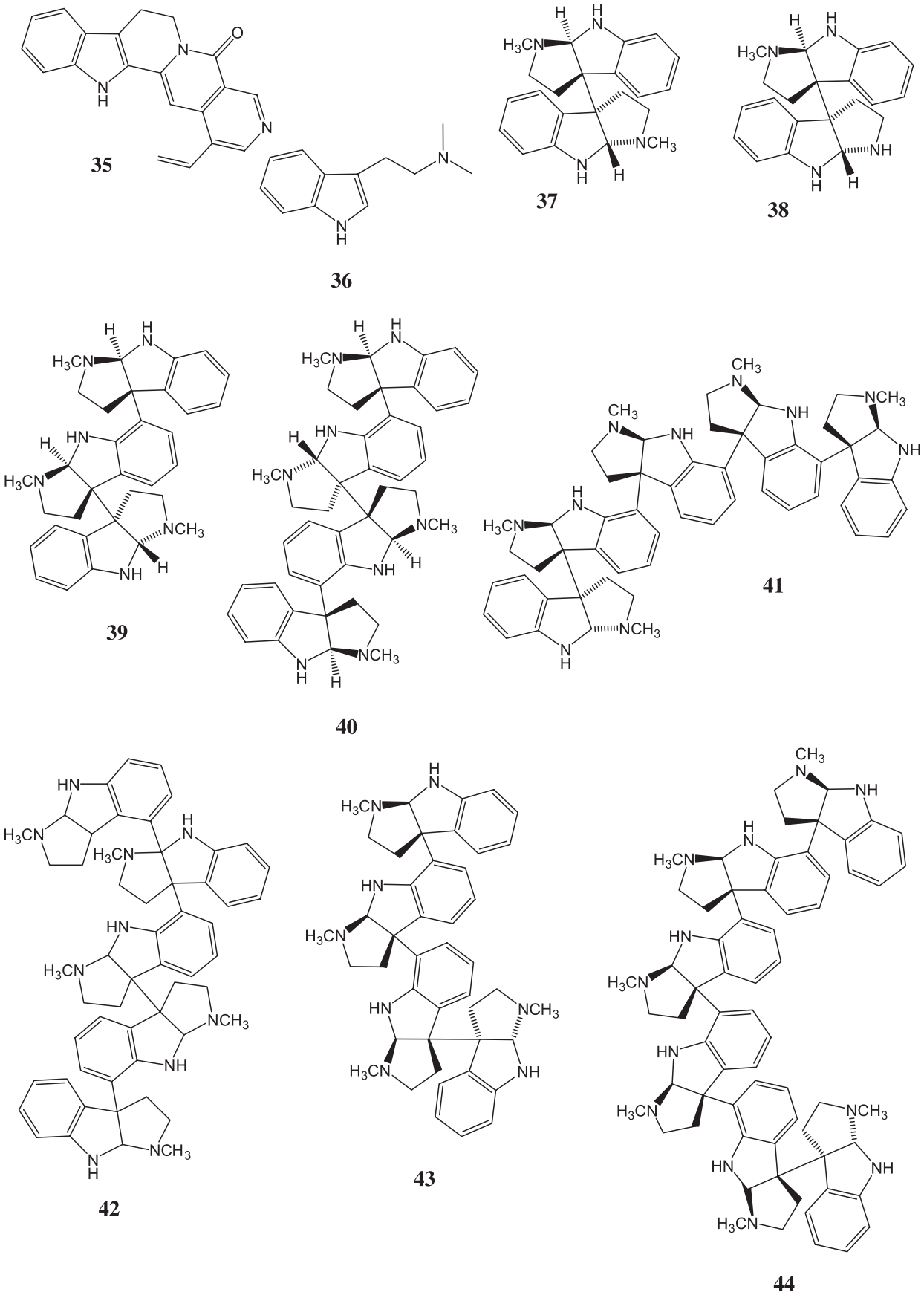
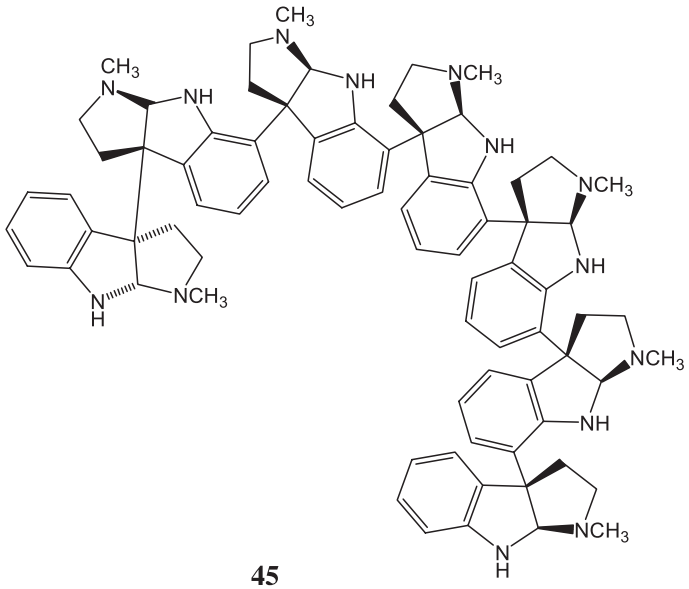


Figure 3. The structures of alkaloids from *Psychotria* species (cont.).



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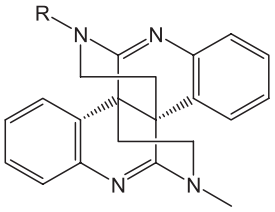
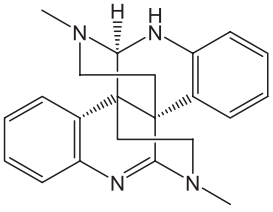


46 R = CH_3
47 R = H



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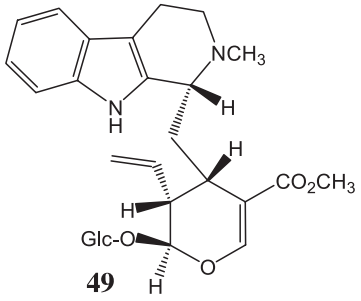

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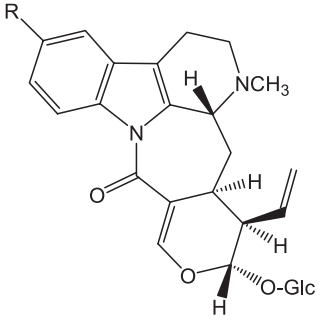
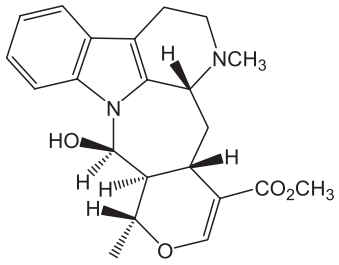


50 R = H
51 R = OH



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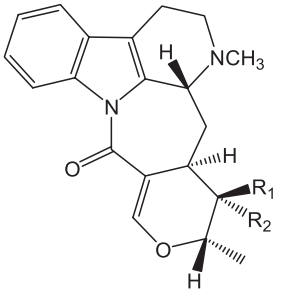
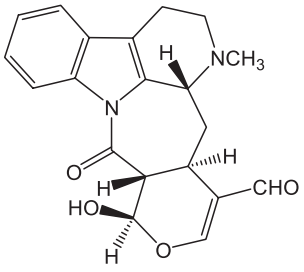


53 R_1 = H R_2 = CHO
55 R_1 = CHO R_2 = H



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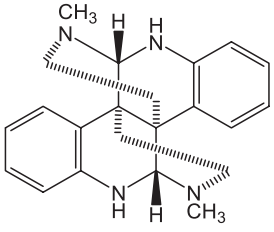

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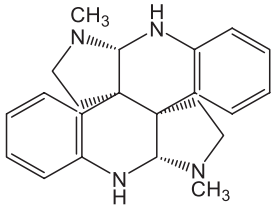

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Figure 3. The structures of alkaloids from *Psychotria* species (cont.).

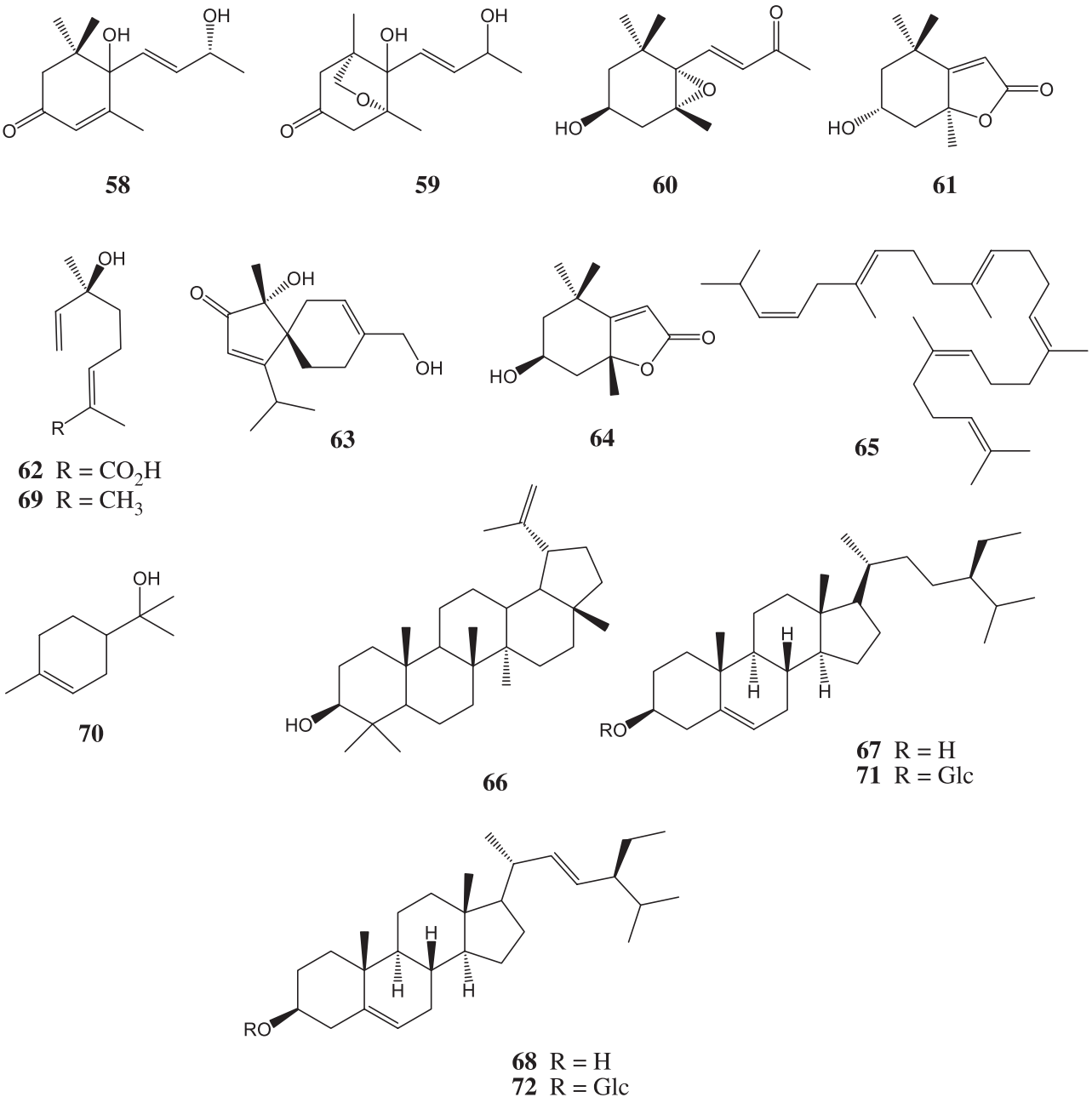


Figure 4. The structures of terpenoids from *Psychotria* species.

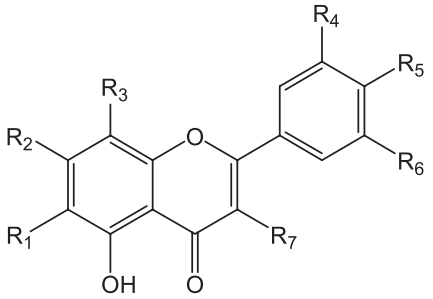
demonstrated highest total flavonoid content.[54,98] From leaves of *P. spectabilis* were isolated quercetin (**73**) and quercetrin (**74**).[13] Two flavonoid glycosides, from *P. rubra,* were identified as 6-hydroxy-luteolin-7-*o*-rutinoside (**75**) and luteolin-7-*o*-rutinoside (**76**).[79] Recently, the chemical study of *P. serpens* allowed the isolation of rutin (**77**), quercetin (**73**), tamarixetin-3-*o*-rutinoside (**78**) and kaempferol (**79**)[81] (Figure 5).

5.4. Coumarins

The phytochemical investigation of *P. vellosiana* aerial parts yielded the scopoletin (**80**).[89] From leaves of *P. spectabilis* were isolated coumarin (**81**), umbelliferone (**82**), and psoralene (**83**) (Figure 6).[13]

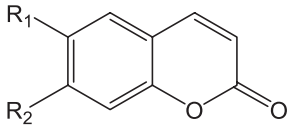
5.5. Tannins

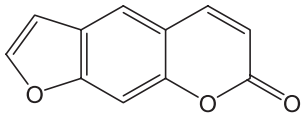
A study realized for *P. carthagenensis*, *P. leiocarpa*, *P. capillacea* and *P. deflexa* showed not only high flavonoid concentration in the extracts, but also the presence of condensed tannins.[20,98] For *P. reevesii* Wall. was realized a screening based on color reactions, high performance liquid chromatography (HPLC) analytical and nuclear



73	R_1 = H	R_2 = OH	R_3 = H	R_4 = OH	R_5 = OH	R_6 = H	R_7 = OH
74	R_1 = H	R_2 = OH	R_3 = H	R_4 = OH	R_5 = OH	R_6 = H	R_7 = *O*-Rham
75	R_1 = OH	R_2 = *O*-Rutinosyl	R_3 = H	R_4 = OH	R_5 = OH	R_6 = H	R_7 = H
76	R_1 = H	R_2 = *O*-Rutinosyl	R_3 = H	R_4 = OH	R_5 = OH	R_6 = H	R_7 = OH
77	R_1 = H	R_2 = OH	R_3 = H	R_4 = OH	R_5 = OH	R_6 = H	R_7 = *O*-Rham-Glc
78	R_1 = H	R_2 = OH	R_3 = H	R_4 = OH	R_5 = OCH_3	R_6 = H	R_7 = *O*-Rutinosyl
79	R_1 = H	R_2 = OH	R_3 = H	R_4 = H	R_5 = OH	R_6 = H	R_7 = OH

Figure 5. The structures of flavonoids from *Psychotria* species.





80 R_1 = OCH_3 R_2 = OH
81 R_1 = H R_2 = H
82 R_1 = H R_2 = OH

83

Figure 6. The structures of coumarins from *Psychotria* species.

magnetic resonance (NMR) spectroscopy. The obtained results revealed the presence of condensed tannins.[99]

5.6. Cyclic peptides

Besides the presence of traditional secondary metabolites, another main chemical constituents are cyclic peptides, especially cyclotides. This peptide group is characterized by a peculiar cyclic structure with approximately 30 amino acids residues with cyclic cystine motif (CCK), conferring them a remarkable stability. All cyclotides sequences described in the literature from *Psychotria* species are presented on Table 2.[100,101]

6. Pharmacological Properties of *Psychotria* Species

6.1. Neurodegenerative diseases

As previously demonstrated on section 4, plants from *Psychotria* genus commonly affect the central nervous system. Recently, several *Psychotria* alkaloids, mainly monoterpene indoles and β-carboline alkaloids have been reported for their inhibitory properties against acetylcholinesterase and monoamine oxidase proteins, which are enzymatic targets related with neurodegenerative diseases.[60,102] Alkaloidal fractions of *Psychotria suterella* and *Psychotria laciniata* as well as two monoterpene indole alkaloids isolated from these fractions were evaluated against monoamine oxidases (MAO-A and MAO-B) obtained from rat brain mitochondria.[59] The monoterpene indole alkaloids lyaloside (**26**) and strictosamide (**22**) exhibited inhibitory effect on MAO-A (IC_{50} 50.04 and 132.5 μg mL^{-1}, respectively) and MAO-B (IC_{50} 306.6 and 162.8 μg mL^{-1}, respectively).[59,60,84] These data confirm the previous study made by McKenna *et al*.[5] which also demonstrated inhibition of MAO by alkaloids compounds present in hallucinogenic "ayahuasca" drink.

Some other effects on the central nervous system involving acetylcholinesterase (AChE), butilcolinesterase (BChE) have also been reported for various other alkaloids of *Psychotria* sp. The β-carboline quaternary alkaloids prunifoleine (**84**) and 14-oxoprunifoleine (**21**) inhibited the enzymes AChE by a non-competitive mode

Table 2. Cyclic peptides identified from *Psychotria* species

Name	Sequence	Plant	Reference
Cyclopsychotride A	-SIPCGESCVFIP-CTVTALLGCSCKSKV-CYKN	*P. longipes*	65
PS-1	GFIPCGETCIWDKTCHAAG---CSCSVANICVRN	*P. suterella*	85
Psyle A	GIA-CGESCVFLG-CFIPG---CSCKSKV-CYFN	*P. leptothyrsa*	64
Psyle B	GIP-CGETCVAFG-CWIPG---CSCKDKL-CYYD	*P. leptothyrsa*	64
Psyle C	--KLCGETCFKFK-CYTPG---CSCSYFP-CK--	*P. leptothyrsa*	64
Psyle D	GIP-CGESCVFIP-CTVTALLGCSCQNKV-CYRD	*P. leptothyrsa*	64
Psyle E	GVIPCGESCVFIP-CISSVLG-CSCKNKV-CYRD	*P. leptothyrsa*	64
Psyle F	GVIPCGESCVFIP-CITAAVG-CSCKNKV-CYRD	*P. leptothyrsa*	64
Psybra 1	GLPICGETCTLGT-CNTPG---CTCSWPI-CTKN	*P. brachiata*	103
Psyde f1[a]	---XC--XCX----CNTSG---CTCK-WX-CTRX	*P. deflexa*	103
Psyde f2[a]	---XCXESCWTSN-CFTSP---CXCX-HP-CTRX	*P. deflexa*	103
Psypoe 1	GSVICGETCFTTV-CNTPG---CYCGAYX-CTRN	*P. poeppigiana*	103
Psysol 1[a]	---XC--XCX----CYTPG---CTCGSYFVCNX-	*P. solitudinum*	103
Psysol 2	GLPICGESCVGGT-CNTPG---CTCTWPV-CTRN	*P. solitudinum*	104
Psysue 1[a]	---XC--XCX----CXIAG---CSCSSALLCVX-	*P. suerensis*	103
Psysue 2[a]	---XC--XCX----CXIAG---CSCSSALLCVX-	*P. suerensis*	103

[a]Partial structure; Cys residues are highlighted in gray.

of inhibition, although inhibited both BChE and MAO by a time-dependent mode of inhibition. In addition, the monoterpene indole alkaloids angustine (**36**), vallesiachotamine lactone (**85**) and vallesiachotamine (**3**) also inhibited BChE and MAO.[59,60] The monoterpene indole alkaloid strictosidinic acid (**11**) isolated from the leaves of *Psychotria myriantha* Mull. Arg. reduced levels of serotonin (5-HT) and DOPA C, a metabolite of dopamine neurotransmitter from the MAO action in rat hippocampus inhibiting probably the precursor enzyme of the biosynthesis of 5-HT. A reduction of 83.5% in 5-HT levels was observed after intra-hippocampal injection (20 μg μL^{-1}). In addition, decreased levels of DOPA C suggests that strictosidinic acid (**11**) have action on the dopaminergic system by inhibiting MAO, which was confirmed by enzymatic assay in rat brain mitochondria. After treatment by intraperitoneal route (10 mg kg^{-1}), a reduction of 63.4% in 5-HT levels and 67.4% in DOPA C values were observed.[69,71] This monoterpene glycosylated indole alkaloid also showed peripheral analgesic and antipyretic activities on mice.[70,105] Those findings suggest that species from genus *Psychotria* might be an interesting source for new MAO inhibitors.

The peptide cyclopsichotride A (Table 2), isolated from the extract of *P. longipes* inhibited the interaction of neurotensin radiolabeled with their membrane receptors on HT-29 cells (intestinal colon carcinoma) and stimulated the increase of calcium intracellular in two different cell lines not expressing neurotensin receptors. It suggests that this compound might be an antagonist of these types of receptors as well as also being able to act via other receptors.[65]

Studies made by Hellinger and co-workers[104] described the bioactivity-guided isolation of a cyclotide from *P. solitudinum* as an inhibitor of a serine-type protease, namely, the human prolyl oligopeptidase (POP). It yielded the isolated peptide psysol 2 (Table 2), which exhibited an IC_{50} of 25 μmol L^{-1}. The enzyme POP plays an important role in memory and learning processes, and it is currently being considered as a therapeutic target for some psychiatric and neurodegenerative diseases, such as schizophrenia and Parkinson's disease.

6.2. Antioxidant and analgesic properties

The monoterpene indole alkaloids psychollatine (**6**) and brachycerine (**14**) isolated from *P. umbellata* and *P. brachyceras*, respectively, presented antioxidant and antimutagenic activity.[42,106,107] In the study made by Both *et al.*,[87] it was described the analgesic properties of isodolichantoside (**49**) isolated from *P. umbellata*. These same analgesic properties have also been reported to alkaloid hodgkinsine (**39**) isolated from another *Psychotria* species, *P. colorata* which is in agreement with the previous study made by Amador *et al.*[108] and Elisabetsky *et al.*,[109] which reported the alkaloid analgesic activity of leaves and flower extracts.

The alkaloid fraction from the ethanol extracts of flowers and leaves of *P. colorata* consisted primarily of a mixture of pyrrolidinoindoline alkaloids quadrigemine C (**40**), calycanthine (**56**), isocalycanthine (**57**) which showed analgesic activity by inhibiting the interaction of naloxone [H_3] with proteins of the cell membrane and also inhibiting

the activity of the enzyme adenylate cyclase in rat. Thus, this suggests an action in opiodergic system since alkaloids did not inhibit the interaction of GMP [H_3]-pnp (guanylyl imidodiphosphate) with the proteins during the Tail-flick analgesic test.[46,47,110]

6.3. Anti-inflammatory activity

Ten *Psychotria* species were collected in the Brazilian Atlantic Forest (*P. pubigera*, *P. ruelliifolia*, *P. suterela*, *P. stachyoides*, *P. capitata*, *P. glaziovii*, *P. leiocarpa*, *P. nuda*, *P. racemosa* and *P. vellosiana*) in order to check if they could inhibit the production of nitric oxide (NO) in macrophages and if they have free-radical scavenging properties. From the evaluated extracts for *in vitro* anti-inflammatory activity, *P. suterela*, *P. stachyoides* and *P. capitata* were the most active in inhibiting macrophage NO production. Interestingly 5,6-dihydro-β-carboline alkaloids were found in all of the ten species evaluated, besides, indol alkaloids were also detected in *P. nuda* and *P. suterela*.[111]

6.4. Anti-protozoal activity

The alkaloids klugine (**28**), cephaelin (**30**) and isocephaeline (**31**) isolated from *P. klugii* presented *in vitro* leishmanicidal activity, being active against *Leishmania donavani.* In addition, the alkaloids **30** and **31** exhibited a potent antimalarial activity against W2 and D6 strains of *Plasmodium falciparum*.[58] The alkaloids obtained from *P. prunifolia* (Kunth) also showed leishmanicidal activity. These alkaloids, 14-oxoprunifoleine (**21**) and strictosamide (**22**) showed selective activity against *Leishmania amazonensi*s, with IC_{50} values of 16.0 and 40.7 μg mL^{-1}, respectively, although they showed no effect on epimastigotes forms of *T. cruzi*.[74]

The compound 1-hydroxybenzoisochromanquinone (psychorubrin) (**86**) and benz[*g*]isoquinoline-5,10-dione (**87**) isolated from the roots and stems of *P. camponutans* by a bioguided fractionation showed inhibition against resistant *Plasmodium falciparum* strains in *in vitro* assays.[45]

6.5. Antiviral activity

Ipecac alkaloids are secondary metabolites produced in the medicinal plant *P. ipecacuanha*. This species is known as a traditional herbal medicine, which was introduced to western medicine over 300 years ago and the syrup is commonly used as emetic for the treatment of patients who ingested poisons. Emetine (**12**) is one of the active compounds found in the syrup and the main alkaloid of Ipecac, which possesses a monoterpenoid-tetrahydroisoquinoline skeleton and is formed by condensation of dopamine and secologanin.[56] Ementine (**12**) was evaluated as an antiviral agent against human immunodeficiency virus (HIV). It inhibited HIV-1 replication by interfering with reverse transcriptase activity and the obtained results showed that in cellular models reduced about 80% of HIV-1 infection. It also blocked HIV-1 infection of RT M184V mutant in *in vitro* reactions with isolated HIV-1RT and intravirion.[95]

Six acetone subfractions of ethanolic extract from *P. serpens* significantly suppressed *Herpes simplex* virus type 1 replication on Vero cells. The viability of cells was not significantly decreased as well as deoxyribonucleic acid (DNA), ribonucleic acid (RNA) and protein synthesis were unaffected showing that inhibitory mechanism of viral replication was not through cytotoxicity and/or blocking of Vero cells growth.[112]

6.6. Cytotoxic activity

Some other bioactive compounds from the polypyrrolidinoindoline alkaloid family have been described as cytotoxic agents. The compounds quadrigemine A (**88**), quadrigemine B (**89**), isopsychotridine C (**90**) and psychotridine (**42**) isolated from *P. forsteriana* leaves showed cytotoxic activity in rat hepatoma cell line (HTC strain) and were more potent than vincristine, an anti-tumor agent.[51,76] These same compounds also inhibited the aggregation of washed human platelets induced by adenosine diphosphate (ADP), collagen and thrombin.[113] In addition, the compounds vatine (**91**), vatamine (**92**) and vatamidine (**93**) exhibited strong cytotoxic activity in rat hepatoma cells and in human leukemia cells.[52]

The bioguided fractionation of *P. serpens* allowed the isolation of the triterpenoid ursolic acid (**94**), which showed cytotoxicity in leukemic cells P-388, L-1210 and A-549 human lung carcinoma. It also showed moderate cytotoxicity in human colon tumor cells (HCT-8) and breast cancer cells (MCF-7).[80]

From *Psychotria* sp. Zhang *et al.*[114] isolated six new triterpenoid saponins called psychotrianosides A-F (**95**-**100**) and some other two compounds already known psychotrianoside G (**101**) and ardisianoside D (**102**). *In vitro* assays showed that the evaluated compounds reduced the viability of tumor cell lines like MDA-MB-231, MCF-7 and HepG2, and inhibited the growth of multi-drug resistant strains such MCF-7/ADM and HepG2/ADM. Among the evaluated saponins, the psychotrianoside C (**97**) showed the most potent cytotoxic effect and also induced cell death by apoptosis.

The alkaloid emetine (**12**) presented cytotoxic and apoptosis effects in leukemia cell lines via mitochondrial pathway.[56,115] When tested with cisplatin (standard chemotherapeutic agent) it increased levels of apoptosis, inducing the expression of several proapoptotic genes and inhibiting expression of survival factors.[56]

The alkaloid psychotripine (**23**), a trimeric pyrroloindoline derivative with a hendecacyclic system bearing a hexahydro-1,3,5-triazine unit, was isolated from the leaves of *P. pilifera*. This compound was evaluated for cytotoxicity in five different tumor cell lines, HL-60 (leukemia), SMMC-7721 (liver cancer), A-549 (lung cancer), MCF-7 (breast cancer) and SW480 (colon cancer) although did not present any significant activity ($IC_{50} > 40$ mmol L^{-1}).[73]

The 1-hydroxybenzoisochromanquinone (psychorubrin) (**86**) isolated from *P. rubra* showed cytotoxic effect on tumor lineage KB. In addition, some other naphthoquinones derived from structural modifications exhibited cytotoxic activity higher than the natural product psychorubrin, thus demonstrating the importance of structure-activity study.[78]

From the species *P. leptothyrsa*, six cyclotides were isolated (Psyle A-F) (see Tables 1 and 2), however only the cyclotides psyle A, C and E showed a potent cytotoxic effect ($IC_{50} = 0.64 > 10$ μmol L^{-1}) in breast cancer cell lines resistant (MCF-7/ADR) or not (MCF-7). It was demonstrated that the presence of cyclotides in MCF-7/ADR cell line significantly increased the cytotoxicity induced by doxorubicin ($IC_{50} = 0.39$-0.76 μmol L^{-1}), revealing a chemosensitization effect of these compounds, as well as being promising against resistant breast cancer cell lines.[64,116]

6.7. Bactericidal and antifungal activity

The compound quadrigemine B (**89**) isolated from *P. rostrata* showed bactericidal activity against *Escherichia coli* and *Staphylococcus aureus*.[76] From the leaves of the same species were isolated some other alkaloids like psychotrimine (**17**) and psychopentamine (**18**), which showed anti-bactericidal activity against resistant gram-positive bacteria *Bacillus subtilis* and *S. aureus*.[77,117]

In a study made by Moraes *et al.*,[111] ten *Psychotria* species (*P. pubigera*, *P. ruelliifolia*, *P. suterela*, *P. stachyoides*, *P. capitata*, *P. glaziovii*, *P. leiocarpa*, *P. nuda*, *P. racemosa* and *P. vellosiana*) were evaluated for antimycobacterial activity, in an attempt to find new antituberculosis agents. From the evaluated extracts the species *P. pubigera*, *P. ruelliifolia* and *P. stachyoides* were the most active against *Mycobacterium*.

From *P. spectabilis* were isolated two diterpenes, solidagenone (**103**) and deoxysolidagenone (**104**), three coumarins, coumarin (**81**), umbelliferone (**82**) and psoralene (**83**), which exhibited antifungal activity against the filamentous fungi *Cladosporium cladosporioides* (Fresen) de Vries and *Cladosporium sphaerospermum* Penzig. Further evaluations of compounds **103** and **83** showed selective cytotoxicity against Rad 52Y mutant yeast strain of *Saccharomyces cerevisiae*.[13]

6.8. Other activities

The indole pyrrolidine alkaloids like psycholeine (**105**) and quadrigemine C (**40**) isolated from *P. oleoide*s were subjected to the interaction study with radiolabeled somatostatin ([125 I] *N*-Tyr-SRIF), inhibition of the enzyme adenylate cyclase and somatostatin secretion of growth hormone (GH) by the rat pituitary cells. Psycholeine (**105**) presented antagonistic properties at the SRIF receptor with an IC_{50} of 10^{-5} mol L^{-1}.[72,118]

7. Ecological Approach of *Psychotria* Species

The production of secondary metabolites may also help the plants to develop and grow in the environment. The monoterpene indole alkaloid brachycerine (**14**), an antioxidant glucosidic indole alkaloid, is involved in the defense of *P. brachycera*s Muell. Arg. against the osmotic/oxidative stress, contributing to the detoxification of hydroxyl radicals and superoxide anions. It was demonstrated that the agents responsible for inducing osmotic stress agents such as sodium chloride, sorbitol and polyethylene glycol lead to the alkaloid accumulation in leaves. Some other agents responsible for inducing oxidative stress such as exposure to aluminum, silver and abscisic acid also increased the amount of brachycerine (**14**). Nascimento *et al.*[119] described that brachycerine in not herbivore deterrent, but is involved in defense by modulating oxidative stress.

The major indole alkaloid *N*,β-*D*-glucopyranosyl vincosamide (**15**) from leaves of *P. leiocarpa* Cham. & Schltdl. showed broad antioxidant activity and may act against oxidative stress generated upon wounding, UV exposure and perhaps other environmental stresses.[97]

The study made by Matsuura and Fett-Neto[97] showed the antioxidant effect of GPV (*N*,β-D-glucopyranosyl vincosamide) (**15**) when evaluated *in vitro* tests against singlet oxygen, superoxide and hydroxyl radicals and *in situ* tests against hydrogen peroxide. It was demonstrated that this alkaloid protects the plant *P. leiocarpa* indirectly against oxidative stress generated in injury, exposure to UV rays and other environmental damage, although not directly against herbivory.[96]

Psychotria plants are rich in secondary metabolites that could be toxic against *Sitophilus zeamais* (Coleoptera:

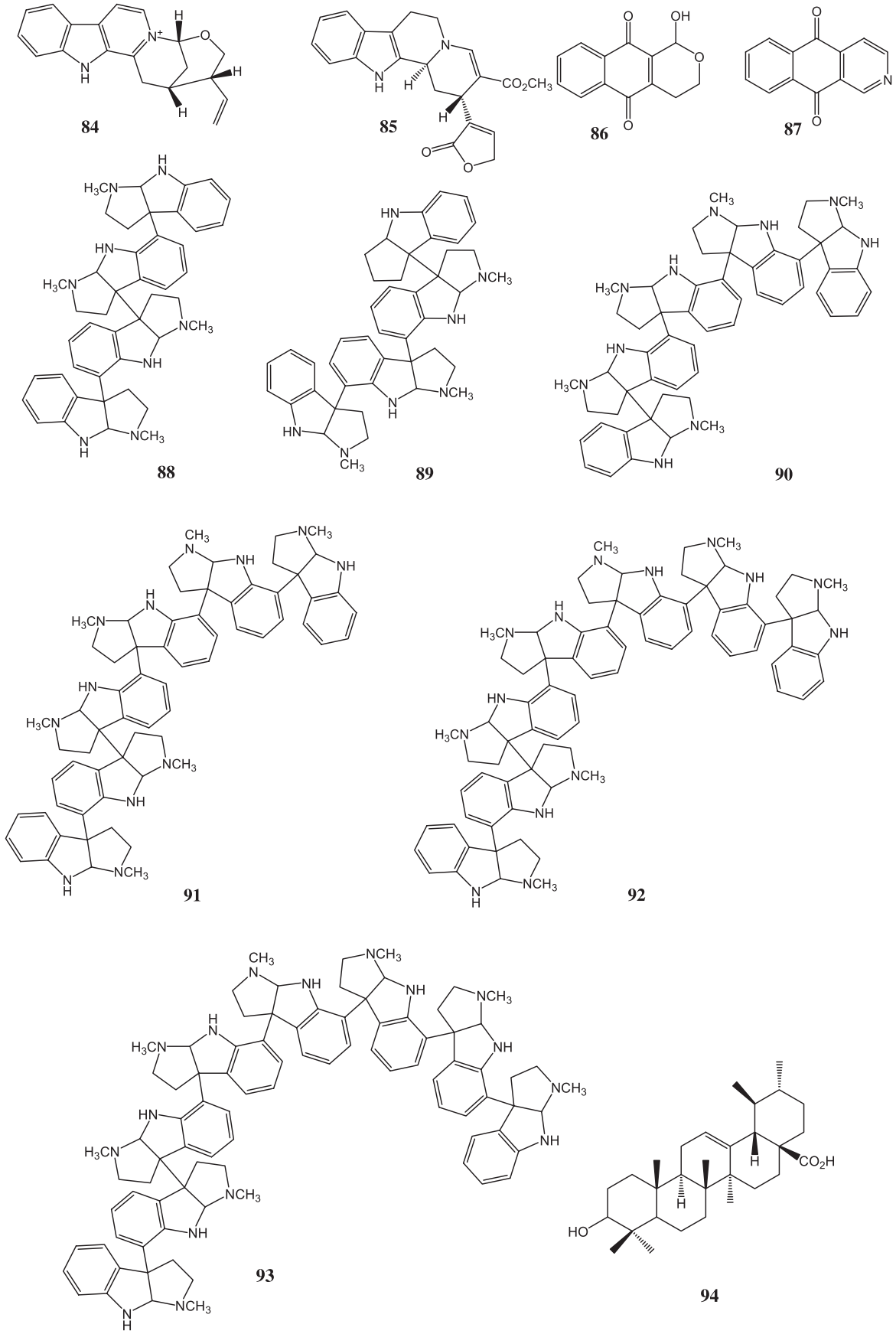
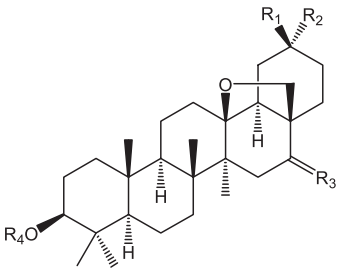
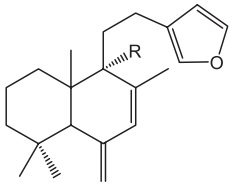


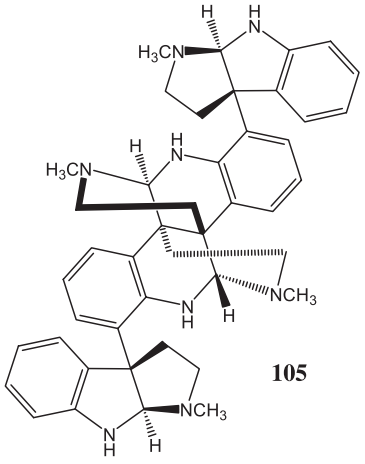
Figure 7. The structures from *Psychotria* species.



	R_1	R_2	R_3	R_4
95	CH_2OH	CH_3	β-H α-OH	Ara
96	CH_3	CHO	β-OH α-H	β-D-Xyl(1→2)-β-D-Glc(1→ 4)-α-L-Ara
97	CH_3	CH_3	O	β-D-Xyl(1→2)-β-D-Glc(1→ 4)-α-L-Ara
98	CH_3	CH_3	β-H α-OH	α-L-Rha(1→4)-β-D-Glc-b-D-Xyl(1→ 2)-β-D-Glc-α-L(1→ 4)-Ara
99	CH_3	CH_3	β-H α-OH	β-D-Xyl(1→ 4)-β-D-Glc(1→ 2)-β-D-Glc(1→ 2)-α-L-Ara
100	CH_2OH	CH_3	β-H α-OH	β-D-Xyl(1→ 4)-α-L-Rha(1→ 2)-β-D-6-acetyl-Glc(1→4)-α-L-Ara
101	CHO	CH_3	β-H α-OH	α-L-Ara
102	CH_3	CH_3	β-H α-OH	β-D-Xyl(1→2)-β-D-Glc(1→ 4)-α-L-Ara



103 R = OH
104 R = H



105

Figure 7. The structures from *Psychotria* species (cont.).

Curculionidae) and *Spodoptera frugiperda* (Lepidoptera: Noctuidae) for maize protection. The study made by Tavares *et al.*[120] demonstrated that extracts (leaves or stems) from *P. hoffmannseggiana*, *P. capitata* and *P. goyazensis* were significantly toxic to these type of insects involving the following parameters such as hatching rate, weight, length, repellence and mortality.

The extract from the leaves of *P. microphylla* showed to be very toxic to the young forms of *Clarias gariepinus*, important species of catfish from Africa. The toxicity of the extract was time and dose-dependent. This extract may be useful in aquaculture to eradicate predators and competitors of wild fishpond in farmed ponds or stocking hatchery fish species commercially cultivated.[121]

Species such as *P. gabriellae* and *P. douarrei* presented the ability to accumulate high amounts of nickel in their sprouts. Metabolites were identified in complexes with Ni including Ni-malonate from *P. douarrei* and the levels for some metabolites were found to correlate with the leaf Ni concentration.[122,123] Studies conducted by Grison *et al.*[124] demonstrated the use of biomass obtained from *P. douarrei* enriched by nickel a catalyst type Lewis acid in organic synthesis as an alternative source of nickel used in the synthesis of antifungal compound monastrol, thus showing its potential to be used in Green Chemistry.

8. Conclusions

As demonstrated in our methods an increasing number of publications revealed a significant interest in *Psycothria* genus in recently years, due to their traditional uses and pharmacological activities. This review presents the main traditional uses as long as pharmacological properties, phytochemistry, chemotaxonomy and ecological approach.

The genus *Psychotria* presents a complex taxonomy and its phytochemical approach became a very useful tool to understand and establish the chemotaxonomy. Several classes of natural products are described for this genus, although, this study highlights the importance of some alkaloids and cyclic peptides, which are involved on central nervous system and neurodegenerative diseases.

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